OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

Ottawa Hull K1A 0C9

(21) (A1) 2,155,956
(86) 1994/02/01
(43) 1994/08/18

(51) Int.Cl.[6] A61D 7/04; A61M 15/08

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Aerosol Delivery Apparatus

(72) Matson, Charles J. - U.S.A. ;

(71) Minnesota Mining and Manufacturing Company - U.S.A. ;

(30) (US) 08/017137 1993/02/12

(57) 23 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61D 7/04, A61M 15/08

A1

(11) International Publication Number: WO 94/17753

(43) International Publication Date: 18 August 1994 (18.08.94)

(21) International Application Number: PCT/US94/01163

(22) International Filing Date: 1 February 1994 (01.02.94)

(30) Priority Data:
08/017,137 12 February 1993 (12.02.93) US

(71) Applicant: MINNESOTA MINING AND MANUFACTURING COMPANY [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventor: MATSON, Charles, J.; P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: HOHENSHELL, Jeffrey, J. et al.; Minnesota Mining and Manufacturing Company, Office of Intellectual Property Counsel, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States: AU, BR, CA, JP, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

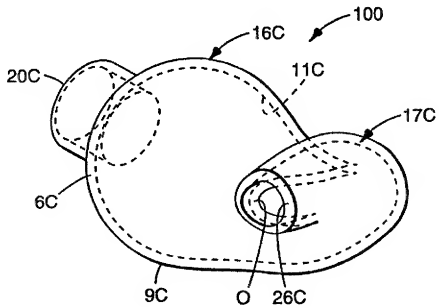
Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

2155956

(54) Title: AEROSOL DELIVERY APPARATUS

(57) Abstract

An aerosol generating device (18) and a conduit (10, 100) for use with the aerosol generating device are disclosed. The conduit and aerosol generating device may be used in a method for administering an aerosol to a large animal, such as a horse.



AEROSOL DELIVERY APPARATUS

Technical Field

This invention relates generally to aerosol delivery methods and devices, and more particularly to an easily insertable apparatus for delivering an aerosol medicament to a large animal, such as a horse, to treat various conditions or ailments.

Background

Large animals suffer from a variety of diseases or illnesses which vary in severity from life threatening to minor ailments. Even minor illnesses may result in consequences (e.g. weight loss) which may adversely affect the economic value of the animal. For example, some horses suffer from chronic obstructive pulmonary disease (see, e.g., F.J. Derksen et al., Airway Reactivity in Ponies with Recurrent Airway Obstruction (Heaves), Journal of Applied Physiology 58(2): 598-604 (1985)). Obstructive lung disease, like asthma, is characterized by acute episodes of airway obstruction due to constriction of airway muscles. The resulting bronchoconstrictive state can result in serious adverse health consequences for the horse due to clinically compromised breathing.

The art is replete with devices and methods for delivering medicaments, vaccines or therapeutic agents to large animals for treatment or cure of diseases or illnesses. Obstructive lung disease in horses has been treated by injecting relatively large doses of medication directly into the blood stream of the horse. Large doses (relative to an aerosol dose) of the medication are often required since the medication has not been specifically targeted to the lungs of the horse. Those larger doses increase the risk of undesirable side effects.

Delivering a medicament or therapeutic agent in aerosol form is becoming increasingly popular. For example, U.S. Pat. No's. 3,915,165 and 4,143,658 describe intratracheal injection systems for injecting dry medicaments in a gaseous suspension into the trachea of an animal in order to treat pneumonia. That system includes a needle (e.g., a catheter) that is inserted into the lumen of the trachea of the animal by puncturing the wall of the trachea. The dry medicaments are then administered through the catheter. Also, a pirbuterol aerosol has been administered through a tube inserted into a chronic tracheostoma in a horse (see, F.J. Derksen et al., Aerosol Pirbuterol: Bronchodilator Activity and Side Effects in Ponies With Recurrent Airway Obstruction (Heaves), Equine Veterinary Journal, 24 (2), pages 107-112 (1992)).

U.S. Patent No. 5,062,423 is directed to a method of and apparatus for delivering a dose of an aerosol medicament to the lungs of a large animal such as a horse. A distal end of an endotracheal-like nasal tube is inserted via a nostril of the horse into its nasal-pharyngeal cavity. The nasal tube prevents aerosolized medicaments from becoming entrained or adsorbed onto the tissue between the opening of the nostril and nasal-pharyngeal cavity of the horse. However, insertion of the nasal tube calls for the operator to place the distal end of the tube in the nasal-pharyngeal cavity of the horse. Such precise placement of the nasal tube may be a difficult task to perform repeatedly.

Summary of the Invention

This invention provides an apparatus for administering an aerosol to a large animal, such as a horse. The apparatus comprises a conduit that is inserted into the nostril of the horse. The conduit is used with an aerosol generating device which preferably generates a respirable aerosol.

The conduit has inner surfaces defining a lumen, outer surfaces, a proximal end, a distal end having an outlet, and connecting surfaces for connecting the conduit to the aerosol generating device.

The conduit has a length which affords locating the outlet in the nasal passageway of the horse. When the large animal comprises a horse, the nasal passageway includes a nasal diverticulum. The conduit should have a sufficient length such that, when the conduit is fully inserted into the nostril, the orifice does not allow passage of the aerosol into the nasal diverticulum. As a result of the length of the conduit, the conduit is both easily insertable into the nostril of the horse and an effective mechanism for delivering a respirable aerosol. Additionally, the length of the conduit renders it less likely to irritate sensitive mucosal membranes of the nasal passageway.

Preferably, the outer surfaces of the conduit are irregular shaped to conform to the irregular shaped surfaces of the horse's nasal passageway. When the outer surfaces conform to the nasal passageway, the conduit is easily placed in the nasal passageway in the proper orientation. Also preferably, the outer surfaces comprise sealing surfaces adapted to abut the tissue surrounding the nostril so that substantially all of the inspiratory airflow through that nostril is directed through the lumen of the conduit.

Once inserted into the nostril, the conduit affords passage of the aerosol in generally the same direction as the inspiratory airflow through the nostril to beneficially entrain the aerosol in the inspiratory airflow. In particular, after insertion of the conduit, the inspiratory airflow through the nasal passageway at the location of the outlet defines a first direction, and the conduit affords passage of the

aerosol through the outlet in a direction that is generally parallel to the first direction.

The conduit preferably has a generally bulbous first section and a second section. The outlet is situated in the second section and the connecting surfaces are situated in the first section. The cross-sectional area of a cross-section in the first section is generally larger than the cross-sectional area of a cross-section in the second section so that inner surfaces of the first section of the conduit form an expansion chamber. The inclusion of an expansion chamber is believed to be particularly desirable when a respirable aerosol is delivered.

The conduit and aerosol generating device described above may be used in a method of administering a respirable aerosol to a large animal, also according to the present invention. The method comprises the steps of (1) providing an aerosol generating device, (2) providing a conduit, (3) connecting the conduit to the aerosol generating device so that the outlet of the conduit is in fluid communication with the aerosol generating device, (4) inserting the distal end of the conduit into the nostril of the large animal; and (5) then actuating the aerosol generating device to deliver the respirable aerosol.

Brief Description of the Drawing

The present invention will be further described with reference to the accompanying drawing wherein like reference numerals refer to like parts in the several views, and wherein:

Fig. 1 is a side view of a head of a horse and the apparatus which includes the conduit and aerosol generating device according to the present invention;

Figure 2 is a side view similar to Fig. 1 with the aerosol generating device omitted and with

portions being broken away to illustrate placement of the conduit of the present invention;

Fig. 3 is an enlarged top plan view of an aerosol-generating device used in conjunction with the conduit of Fig. 2 which illustrates portions of the conduit according to an aspect of the present invention with the rest of the conduit broken away;

Fig. 4 is a cross-sectional view taken generally along line 4-4 of Fig. 3;

Fig. 5 is a perspective view of one embodiment of a conduit according to the present invention;

Fig. 6 is a sectional view of the conduit of Figure 5 taken approximately along line 6-6 of Figure 5;

Figure 7 is a schematic illustration of the position of the conduit of Figure 5 within the nostril of a horse;

Figure 8 illustrates test results for several different experimental conduits;

Figure 9 is a perspective view of the conduit of Figure 5 attached to an aerosol generating device different than the aerosol generating device shown in Figures 3 and 4;

Figure 10 is a partial sectional view of the aerosol generating device of Figure 9 illustrating one embodiment of an airflow indicator;

Figure 11 is a sectional view of portions of an aerosol generating device that is slightly different than the aerosol generating device of Figure 10 and which shows an optional orienting mechanism;

Figure 12 is a perspective view of another embodiment of conduit according to the present invention;

Figure 13 is a top view of the conduit of Figure 12;

Figure 14 is a side view of the conduit of Figure 12, with the exception that an optional finger

rest with groove for use with the orienting mechanism of Figure 11 has been added;

Figure 15 is a distal end view of the conduit of Figure 12;

Figure 16 is a partial sectional, schematic top view of the conduit of Figure 13 schematically illustrating the position of the conduit within the nostril of a horse; and

Figure 17 is a partial sectional, schematic side view of the nostril and conduit of Figure 16.

Detailed Description

Referring now to Figures 1 through 7 and 9 of the drawing, there is shown one embodiment of a conduit according to the present invention generally designated by reference character 10. As shown in Figures 1 and 2, portions of the conduit 10 are inserted into a nostril of the large animal, after which the conduit 10 may be used to administer an aerosol to the large animal.

As used herein, the phrase, "large animal" includes but is not limited to equidae, bovidae, cervidae, cetaceans and other domestic and wild non-primate mammalian species. Particular examples not intended to be limiting include horses, goats, cattle, deer, sheep and dolphins. The conduit 10 is particularly suitable for use with a horse 14. The phrase "large animal", however, specifically excludes humans.

The conduit 10 may be used with an aerosol generating device 18 for generating an aerosol. As used in this application, when used alone, the term "aerosol" is used broadly and means a gaseous suspension or solution of dispersed solid or liquid particles. As used herein, the term "aerosol" includes sprays, colloids, mists and respirable aerosols. The aerosol may be in suspension, solution or dry powder form. An aerosol may comprise a medicament,

therapeutic agent, growth promotor, prophylactic agent or a nutritional agent. Examples of aerosols include medicaments, drugs and vaccines.

Preferably the aerosol generating device 18 generates a respirable aerosol which specifically targets the lungs of an animal. As used in this application, the phrase "respirable aerosol" means an aerosol having a component that is ultimately delivered to the lungs of the large animal, as opposed, for example, to an aerosol with droplets that are designed to be deposited on the surfaces of the animal's nasal passages and subsequently adsorbed onto the tissue of the nasal passages. Preferably, using the horse 14 as an example, the component will be delivered beyond the upper respiratory tract and to the peripheral lung field (e.g. the alveoli of the lung). Typically the component of a respirable aerosol medicament includes an appreciable amount of medicament particles having a size of less than about thirty (30) micrometers, and preferably less than about ten (10) micrometers when measured using a multistage cascade impactor (generally available from Anderson Samplers, of Atlanta, Georgia) according to the method described by Chowtan, Z. T. et al. in "Report and Recommendations of the USP Advisory Panel on Aerosols on the USP General Chapter <601> on Aerosols" Pharmacopeial Forum 1991; 17(2), Pps. 1703-1713. For purposes of this application, an "appreciable amount" of a respirable aerosol medicament means an amount capable of eliciting a therapeutic or physiological response, as opposed to a mere trace or negligible amount.

The conduit 10 has outer surfaces 9, a proximal end 20, a distal end 26 having an outlet O, and inner surfaces 11 which preferably afford passage of an aerosol generated by the aerosol generating device 18 through the conduit 10. The inner surfaces 11 define a lumen extending between the proximal 20 and

distal 26 ends, and open to the outer surfaces 9 at the outlet O.

The conduit 10 also includes connecting surfaces preferably adjacent the proximal end 20 of the conduit 10. The connecting surfaces may be used to removably connect the conduit 10 to the aerosol generating device 18 so that the outlet O of the conduit 10 may be placed in fluid communication with the aerosol generating device 18.

The conduit 10 comprises first 16 and second 17 sections with the outlet O situated in the second section 17 and the connecting surfaces situated in the first section 16. The edge of the conduit 10 forming the distal end 26 is smoothly rounded in order to facilitate introduction of the conduit 10 into the nostril N of the horse 14 and to avoid irritating tissue.

Figure 7 is a schematic illustration of the conduit 10 positioned within the end of the respiratory passageway 1 of a horse 14. As schematically shown, the nasal passageway 1 of the horse 14 begins at the nostril N of the horse and includes the nasal diverticulum 5 and the ventral passage 7.

The conduit 10 has a length which affords locating the outlet in the nasal passageway of the large animal. As used in this application, the phrase "nasal passageway of the large animal" means those surfaces between (1) the outer end of the animal's nasal tract (e.g. the opening of the animal's nostril) and (2) the juncture of the nasal-pharyngeal cavity.

Locating the outlet O of the conduit 10 in the nasal passageway as opposed to the nasal-pharyngeal cavity is believed to facilitate convenient, efficient, and effective insertion of the conduit 10 into the nostril of the horse 14. The conduit 10 should have a sufficient length such that, when fully inserted, the orifice O does not allow passage of the aerosol (e.g. a respirable medicament) into the nasal diverticulum 5 of

the horse 14 (where a substantial amount of the medicament may be wasted, or where the uptake of the medicament may be substantially delayed). Preferably, when the conduit 10 is fully inserted into the nostril of the horse, the outlet O is located in the nasal vestibule and is bounded medially by the nasal septum, dorso-laterally by the alar fold and ventrally by nasal mucosa. The orifice O should not project excessively far into the nasal passageway to afford ease of insertion of the conduit 10 and to avoid irritating sensitive mucosal membrane tissue of the nasal passageway/cavity that may cause discomfort for the horse 14.

The outer surfaces 9 of the conduit 10 comprise sealing surfaces 6 adapted to abut the tissue surrounding the nostril N of the horse 14 such that substantially all of the inspiratory airflow through the nostril is directed through the lumen of the conduit 10. Additionally, the amount or degree of insertion of the conduit 10 into the nostril is limited by the sealing surfaces 6 to avoid accidental over insertion or lodging of the conduit 10 in the nasal passageway.

The sealing surfaces 6 are preferably sized and shaped (e.g. the semi-spherical shape shown in the figures) to abut and cooperate with the socket-like opening of the horse nostril. However, optionally the sealing surfaces may comprise other shapes such as a frusto-conical shape so long as they generally conform to the surfaces.

The sealing surfaces 6 form a seal with a nostril so that substantially all of the inspiratory airflow through that nostril also flows through the conduit. Directing substantially all of the inspiratory airflow through conduit is believed to beneficially entrain the aerosol into the inspiratory airflow to increase the likelihood that the aerosol will completely traverse the respiratory system of the

animal and become entrained on the peripheral surfaces of the lung.

The outer surfaces 9 forming the first section 16 are preferably constantly curved to form a bulbous first section. Preferably, the first 16 and second 17 sections of the conduit 10 have cross-sections with arcuate portions which reflect the irregular shape of the conduit. Also preferably, the cross-sectional area of a cross-section in the first section 16 is generally larger than the cross-sectional area of a cross-section in the second section 17.

When an respirable aerosol is passed through the lumen of the conduit 10, the inner surfaces 11 of the first section 16 of the conduit 10 form an expansion chamber to afford expansion and maturation of the respirable aerosol prior to expulsion from the conduit 10. The expansion chamber affords many potential advantages: (1) it allows particles or droplets generated by the aerosol generating device 18 that would not otherwise reach the lungs of the animal (e.g. large particles) to "drop out" of the aerosol, (2) it slows down the speed of the individual particles or droplets in the aerosol before they leave the conduit, and (3) if the aerosol generating device 18 utilizes a propellant, the expansion chamber allows some propellant to evaporate from the aerosol prior to leaving the conduit.

As an example not intended to be limiting, the conduit 10 should have an overall length L (see Figure 6) of about 5.4 inches, a generally elliptical outlet O having a width of about 1.14 inches and a height of about 0.77 inches, a maximum outer diameter of about 2.64 inches in the first section, an opening adjacent the proximal end 20 having an inner diameter of about 0.875 inches, an axial length from the proximal end 20 to a point on the axis of the conduit 10 which defines the maximum outer (radial) diameter of

about 1.95 inches, and a generally constant thickness of about 0.2 inches.

The aerosol-generating device 18 includes a canister 22 of the type for dispensing a metered dose of a medicament through a hollow stem 24. A metered dose is dispensed from such a canister 22 when a metering valve mechanism (not shown) is actuated, which typically occurs when the stem 24 is moved relative to the canister 22. For example, suitable canisters 22 are described in U.S. Pat. No's. 4,819,834 and 3,738,542. Canisters 22 of this type include a propellant and multiple doses of the medicament, which are discharged in predetermined standard amounts via a metering valve mechanism (not shown) actuated either by relative inward movement of the stem 24, or relative outward movement of the stem 24 following inward movement. Such metering valve mechanisms are typically designed to deliver a predetermined volume of the aerosol dose, for example, 50 or 63 microliters, each time the mechanism is actuated. Alternatively, the aerosol generating device may comprise a nebulizer or dry powder inhaler.

The connecting surfaces are connected to a means for connecting the conduit 10 to the canister 22. The means comprises a body 33 having an air passageway 34 in fluid communication with the lumen of the conduit 10, and an air opening 36. The body 33 is connected to the conduit 10 at end 60.

A stem receptacle 38 is provided in the body 33 outside and generally adjacent the air passageway 34 for receiving the stem 24 of the canister 22. A hollow tube 40 preferably extends generally transversely or laterally across the air passageway 34 from a portion of the wall of the passageway 34 adjacent the stem receptacle 38. The terms, "transversely" and "laterally" are used in the same manner as their use in U.S. Patent No. 5,062,423.

The hollow tube 40 is in fluid communication with a hollow stem 24 received in the stem receptacle 38, and the stem receptacle 38 seals along the sides of the stem 24 so that a metered dose discharged from the canister 22 is forced into the hollow tube 40. The arrangement is such that, when the canister 22 is pushed toward the stem receptacle 38, the stem 24 is moved toward the canister 22 to actuate the metering valve mechanism and discharge a dose into the hollow tube 40.

An orifice 42 is provided in the hollow tube 40, and opens into the air passageway 34 from the bore of the tube 40 for delivering a metered aerosol dose into the inhalation air stream flowing through the air passageway 34. The orifice 42 preferably opens through the hollow tube 40 along the central longitudinal axis of the air passageway 34 in the direction toward the conduit 10 (rightwardly in Fig. 4) to facilitate entraining the aerosol medication in the air stream, while minimizing the amount of medication deposited along the walls of the air passageway 34 of the aerosol-generating device 18. Preferably, the hollow tube 40 extends completely across the air passageway 34 and the orifice 42 is positioned along the midpoint of the hollow tube 40.

The hollow tube 40 may be formed of a narrow stainless steel tube (also 40) having an outside diameter of approximately 0.049 in. (1.2mm), and an inside diameter of approximately 0.033 in. (0.81mm), which is appropriate for preventing premature aerosolization of a metered dose inside the hollow tube 40. The orifice 42 preferably has a circular cross-section of approximately 23 thousands of an inch (584 micrometers) diameter.

A canister housing 46 may be provided for securing canisters 22 (e.g. replacements) for operation of the aerosol-generating device 18. The canister housing 46 is detachably or "releasably" mountable on

the body 33 of the aerosol-generating device 18 via, for example, a bayonet fastening mechanism illustrated generally at 48. Alternatively, the canister 22 may be simply slip fit to the body 33.

A triggering mechanism 50 may also be provided for moving the canister 22 toward the stem receptacle 38, thereby moving the stem 24 of the canister 22 toward the canister 22 to actuate the metering valve mechanism and discharge an aerosol dose into the hollow tube 40. The triggering mechanism 50 may include a push button 52 for releasably pressing the canister 22 toward the stem receptacle 38 to discharge a metered dose, and a resilient coil spring 54 pressing against both the push button 52 and the housing 46 to bias the push button 52 toward its ready position.

An air flow indicator is preferably mounted in the air passageway 34 of the body 33 to visibly, tactily or audibly indicate when a metered dose should be discharged from the canister 22 for optimum effect. For example, the indicator may include a vane 56 (Fig. 4) movable (pivotable) in response to air flow through the lumen of the conduit 10. A window 57 may be provided in the body 33 of the aerosol-generating device 18 so that the vane 56 may be observed visibly. Such a vane 56 may readily be adapted to generate an audible signal by striking the wall of the air passageway 34 when reduced pressure causes it to pivot.

The proximal end 20 of the conduit 10 may be attached to the body 33 by any suitable manner. Preferably, while the body 33 should be firmly attached to the conduit 10, the body 33 should readily separate from the conduit 10 if an animal suddenly violently shake or move its head. For example as shown in Figure 3, the conduit 10 is constructed from a resilient, flexible material which affords stretching the distal end 20 over an end 60 of the body 33 to form a tight friction fit. Optionally, a radial clamp may be used

to enhance this friction fit. The mounting assembly shown in Figure 3 constitutes one illustrative design of a tube-connecting means, although other types of connections are also contemplated.

In use, the air opening 36 and air passageway 34 are preferably in fluid communication with the lumen of the distal end 20 of the conduit 10. As a result, air is permitted to flow freely through the air opening 36 of the aerosol-dispensing device 18. During inhalation through the conduit 10, air travels inwardly from the air (inlet) opening 36 through the air passageway 34 and lumen of the first section 16 which functions as an expansion chamber to afford expansion of the dose of aerosolized medicament. From the lumen of the first section 16, the aerosol (e.g. aerosolized medicament) flows into the lumen of the second section 17 and then through the respiratory passages 1 of the horse 14 and ultimately to its lungs (if a respirable aerosol is sought to be delivered).

Figures 9 and 10 illustrate another embodiment of a body for associating the conduit (e.g. 10) with a canister (e.g. 22A), generally designated by reference character 33A. The body 33A includes many features similar to the body 33 which are identified by the same reference number to which the suffix "A" has been added.

Like the body 33 and canister 22, the body 33A and canister 22A include a hollow stem 24A, a stem receptacle 38A, a hollow tube 40A with orifice 42A, and an end 60A adapted to be connected to the conduit 10. The body 33A includes a trigger 55 movable relative to the rest of the body 33A between cocked and fired positions. The canister 22A is slip or friction fit to the body 33A. Bail 51 also assists in coupling the canister 22A to the body 33A.

The bail 51 is operatively connected to the trigger 55 and moves the canister 22A relative to the stem 40A when the trigger 55 is manually moved from the

cocked toward the fired position so that the trigger 55 actuates the stem 24A. The spring within the canister 22A returns the trigger 55 from the fired to the cocked position after the canister 22A is actuated.

Unlike the body 33, the body 33A includes a handle 53 which affords a pistol-like grip. When the conduit 10 is coupled to the body 33A, the pistol-like grip provided by the handle 53 affords ease of insertion of the distal end portion of the conduit 10 into the nostril of the animal, as the manipulations of the handle 53 which are required when inserting the conduit 10 are believed to be well within the average user's range of motion (e.g. wrist, hand and arm movements). Additionally, the handle 53 allows the user to firmly hold the body 33A and control the conduit 10 when the trigger 55 is squeezed.

Also unlike body 33, a proximal end portion of the air passageway 34A of the body 33A is situated at generally a right angle relative to the distal end portion of the air passageway 34A. This configuration of the air passageway 34A restricts the chance that an object (e.g. a user's hand) will restrict the passage of inspirator airflow through passageway 34.

The airflow indicator for the body 33A comprises an elastomeric balloon member 58 in fluid communication with the air passageway 34A. As the animal inhales through air passageway 34A, the pressure within air passageway 34A drops which causes the balloon 58 to collapse. Optimally, a user will actuate the trigger 55 when the balloon is collapsed.

Figure 11 illustrates another embodiment of a body for associating the conduit (preferably conduit 100 described below) with a canister (e.g. 22B), generally designated by reference character 33B. The body 33B includes many features similar to the body 33 which are identified by the same reference number to which the suffix "B" has been added.

Like the body 33 and canister 22, the body 33B and canister 22B include a hollow stem 24B, a stem receptacle 38B, a hollow tube 40B with orifice 42B, an air passageway 34B, and an end 60B adapted to be connected to the conduit. As an example not intended to be limiting, the air passageway 34B may have a diameter of about 0.67 inches, a wall thickness of about 0.2 inches and an overall length of about 4.5 inches. The handle 53B may have a height of about 3.6 inches (measured from the bottom to the walls of the air passageway 34B) and a width of about one inch.

The handle 53B includes rear curved surfaces 71 that are adapted to approximate the surfaces of a user's palm just below the thumb. Those palm surfaces directly abut the surfaces 71 when the body 33A is grasped in a pistol-like fashion. As described in greater detail below, the body 33B optionally includes an orienting means 72 generally adjacent end 60B for use with an optional finger rest.

Like the body 33A, the body 33B includes a trigger 55B movable relative to the rest of the body 33B between cocked and fired positions. Bail 51B is operatively connected to the trigger 55B and moves the canister 22B relative to the stem 40A when the trigger 55B is moved from the cocked toward the fired position.

Unlike the body 33, the body 33B includes a vane 56B situated within a visibly transparent cylindrical housing 59. The vane 56B is adapted to deflect (e.g Figure 11 dashed lines) in response to airflow through the passageway 34B (Figure 11, dotted lines) to indicate that inspiratory airflow is traveling through the passageway 34B.

Figures 13 through 17 illustrate a second, preferred embodiment of conduit according to the present invention generally designated by the reference character 100. The conduit 100 has features similar to the conduit 10 which are identified by the same

reference character to which the reference character "C" has been added.

Like the conduit 10, the conduit 100 includes a generally bulbous-shaped first section 16C, a second section 17C, proximal 20C and distal 26C ends, an outlet O, sealing surfaces 6C, inner surfaces 11C defining a lumen and outer surfaces 9C.

The shape of the conduit 100 is slightly different than the shape of the conduit 10. The outer surfaces 9C are irregular shaped and are adapted to generally conform to the irregular shaped surfaces of the horse's nasal passageway.

Figures 16 and 17 schematically illustrate how the outer surfaces 9C conform to the irregular shaped surfaces of the horse's nasal passageway after it has been inserted within the nasal passageway (e.g. into the nostril). The outlet O efficiently bypasses the alar fold 3 and preferably rests in the same position as that position of the conduit 10 described above with reference to Figure 7.

Much of the outer surfaces 9C abut the tissue of the nasal passageway 1. Again, the conduit 100 has a sufficient length such that the orifice O does not allow passage of the aerosol into the nasal diverticulum 5 of the horse 14.

The lumen of the conduit 100 defines a central axis A (Figure 13) extending from generally adjacent the connecting surfaces to the outlet O. The portion of the axis A generally adjacent the connecting surfaces (102 in Figure 13) is situated at an angle Beta (β) of between about 0 and about 180 degrees (and most preferably about ninety degrees) relative to the portion of the axis generally adjacent the outlet O (103 in Figure 13).

With the sealing surfaces 6C abutting the nostril N, the conduit 100 directs substantially all of that nostril's inspiratory airflow through the lumen 11C. Also, the conduit 100 affords passage of an

aerosol in generally the same direction as the inspiratory airflow through the nostril. Such action is believed to beneficially entrain the aerosol in the inspiration airstream, and is particularly desirable when a respirable aerosol is to be delivered.

The inspiratory airflow through the nasal passageway 1 at the location of the outlet O defines a first direction 101 (Figure 16). The conduit 100 affords passage of the aerosol through the outlet O in a direction that is generally parallel to the first direction to allow the aerosol to be beneficially entrained in the inspiration airstream.

Since the outer surfaces 9C of the conduit 100 generally conform to the irregular shaped surfaces of the horse's nasal passageway 1, the outer surfaces 9C tend to facilitate proper orientation of the conduit 100 within the nasal passageway 1. It is believed that a user will be readily able to discern whether the conduit 100 is properly oriented within the nostril due to the "feel" of the conduit 100 when it is within the nasal passageway 1.

To further facilitate proper orientation of the conduit 100 and ease of administration of the aerosol, the conduit 100 may optionally include a finger rest 75 (Figure 14) which includes a groove 76 adapted to receive the orienting means 72 described above in conjunction with the body 33B (Figure 11). When the proximal end 20C of the conduit 100 is connected to the body 33B, the orienting means 72 is received within the groove 76 to ensure that the body 33B (including the handle 53B) is properly oriented relative to the conduit 100. A user's finger may be placed on the finger rest to augment the user's control of the conduit 100 as it is being inserted into the nostril.

As an example not intended to be limiting, the first section 16C of the nasal conduit 100 may have a maximum outer diameter of approximately 2 3/8 inches,

the second section 17 may have an outer diameter at the outlet O of approximately 7/8 inches, and the conduit 100 may have a generally constant overall thickness of about 1/8 inches. The generally cylindrical portion of the conduit 100 generally adjacent the proximal end 20C has an outlet diameter of about 0.85 inches tapering to 0.78 inches just prior to opening into the expansion chamber. The conduit 100 has a length as measured horizontally from the extreme left to the extreme right in Figure 14 of about 4 5/8 inches, and a height as measured vertically from the extreme top to the extreme bottom in Figure 14 of about 3 1/8 inches.

The bodies 33, 33A and 33B may be constructed from any suitable material, and preferably a material suitable for medical purposes. Examples include metals and plastics. If an aerosol medicament is dispensed from the canister, the material should be compatible with the medicament.

The conduits 10 and 100 are preferably constructed from a flexible, resilient material. The material should be sufficiently flexible to generally conform to the inner surfaces of the horse's nasal cavity, such as the nasal cartilage and nasal mucosa, to restrict irritation of sensitive tissue. Also, the material should be sufficiently resilient to avoid or restrict collapse when a portion of the conduit (e.g. 100) is placed in the nasal passageway of the horse so that the outlet O remains in fluid communication with the aerosol generating device 18. Materials that may be used to construct the conduit include but are not limited to elastomers (e.g. rubber-like material), plastics and plastic-like materials. Particular examples include polyethylene (e.g. an FDA approved LDPE or EVA Copolymer polyethylene), a silastic, a flexible polyvinylchloride, or a flexible polyester. The conduits may be constructed using any suitable procedures, such as injection molding, dip molding, spin molding, and blow molding. The conduits 10 and

100 may be constructed using the techniques described in Example 1 below.

The conduit 100 may be used with an aerosol generating device comprising the body 33B and canister 22B in a method of administering a respirable aerosol to a large animal, also according to the present invention. The method comprises the steps of (1) providing an aerosol generating device (e.g. 18), (2) providing a conduit (e.g. 10 or 100), (3) connecting the conduit to the aerosol generating device so that the outlet O of the conduit is in fluid communication with the aerosol generating device, (4) inserting the distal end of the conduit into the nostril of the large animal; and (5) then actuating the aerosol generating device to deliver the respirable aerosol.

TEST RESULTS

A series of tests were performed on several different sizes and shapes of conduits to determine their aerosol output or "throughput". The first shapes of nasal conduits that were tested were three hydrometer bulbs or "eyedropper" conduits. A small, medium and large "eyedropper" shape were tested. A hole was cut in the large end of each of the eyedroppers. The small, medium and large bulbs had lengths, maximum outer diameters and outlet opening diameters of 2 1/16, 2 13/16, 3 1/4; 1 13/16, 2 3/8, 2 9/16; 1/2, 1/2, 5/8 inches respectively. The small conduit had a volume of about forty-one (41) milliliters, the medium approximately ninety-five (95) milliliters, and the large about one-hundred-twenty (120) milliliters.

A second conduit configuration was generally spherical (69 ml) and had an overall length of about 2 5/8 inches, an orifice outlet diameter of about 11/16 inches, a maximum outer diameter of about 2 3/16 inches, and a volume of about sixty-nine (69) milliliters.

An aerosol generating device similar to the device shown in Figure 1-3 was utilized. The aerosol generating device utilized a Maxair™ canister with a 50 microliter valve. Four actuations of 200 micrograms delivery per actuation were utilized. Airflow at 50 LPM was drawn through the actuator-conduit with four actuations of the aerosol canister occurring during each test. A total of three tests were performed for each configuration of the conduits and the results were based on the average of these three tests.

Figure 8 is a bar graph illustration of the results of these tests. The large conduit allowed 98% of the predicted aerosol output to pass through. As conduit size decreased, aerosol output likewise decreased (medium 76% and small 65%). The spherical shaped nasal conduit allowed 71% of the predicted output to pass through.

The four nasal conduits mentioned above were coupled to an aerosol generating device (similar to reference character 18 shown in Figures 2 and 3) and were tested on live horses. It was found that the large and small nasal conduits did not have a preferential fit with the anatomy of the external nostril. The spherical nasal conduit had the least desirable fit as it did not form a preferred seal with the surfaces surrounding the nostril of the animal. The medium sized nasal conduit was the most preferred as it fit the external nostril of both ponies and horses.

A second test on the medium nasal conduit was performed to test its ability to deliver an experimental, investigational dose of a bronchodilator (e.g. a dose of 3200 micrograms of the pirbuterol acetate bronchodilator, sold under the name Maxair™ Inhaler generally available from 3M Pharmaceuticals of St. Paul, Minnesota).

A pony with sufficiently compromised airways due to COPD (chronic obstructive pulmonary disease) was

instrumented for measuring airway mechanics. The pulmonary function of the pony was tested both before and after the administration of a drug according to the following method (See F.J. Derksen et al., Aerosol Pirbuterol: Bronchodilator Activity and Side Effects in Ponies with Recurrent Airway Obstruction (Heaves), Equine Veterinary Journal 24(2): 107-112 (1992); and F.J. Derksen et al., Pulmonary Function in Standing Ponies: Reproducibility and Effect of Vagal Blockade, Am. J. Vet Res. 43, 598-602 (1982).

An esophageal balloon, attached to a catheter is placed into the distal third of the esophagus and connected to a calibrated pressure transducer (Validyne Model DP45-34 generally available from Validyne, of Northridge, CA). The position of the esophageal balloon is adjusted to obtain the maximum change in pleural pressure during tidal breathing. A #5 Fleisch pneumotachograph (available from Gould, Inc. of Minneapolis, Minnesota) is mounted on a face mask which covers the external nares. The face mask is taped to the face to prevent leaks. The Fleisch pneumotachograph is connected to a pressure transducer (Validyne Model DP43-22) that provides a signal proportional to airflow. The flow signal passes to a Buxco pulmonary function computer (available from Buxco Electronics, Inc., of Sharon, Connecticut) that integrates the signal to provide tidal volume. Flow, tidal volume and transpulmonary pressure (ΔP_{pl}) during breathing are processed by the lung function computer to provide a breath-by-breath measurement of pulmonary resistance (R_L) and dynamic compliance (C_{dyn}). Thirty breaths are used to calculate (ΔP_{pl}), (R_L) and (C_{dyn}) at each observation time point. Pulmonary function measurements are made prior to administration of the aerosols to qualify the pony for testing and to obtain baseline values.

Table 1 illustrates the results obtained from testing the medium sized nasal conduit. Within nine to

ten minutes after administration of the medicament, significant bronchodilation of the airways had occurred. The results indicate that the aerosol dosage or bolus effectively traverses the labyrinth of the nasal cavity in sufficient quantity to reach the active sites within the lung to induce bronchodilation.

Table 1

Pulmonary Function Tests of COPD Pony Treated With 3200 μg Pirbuterol Acetate Using Actuator-Conduit System**

(Mean values during each time period)

Time	MAX ΔP_{pl}	R_L	C_{dyn}
Pre-Treatment	37.1	5.47	0.119
Post-Treatment 0:49-1:45	17.4	1.40	0.929
1:55-2:37	9.2	1.31	0.738
2:52-3:53	11.5	1.37	0.665
3:55-4:57	20.6	1.46	1.308
4:59-5:57	13.4	1.27	1.524
5:59-6:24	13.2	1.23	2.233
7:11-7:47	10.6	0.94	2.381
8:05-8:49	11.6	1.14	4.835
8:50-9:18	11.8	0.90	3.193
Post-TX Mean	13.3	1.22	1.978
Percent Change from Pre-Tx mean	64.0% (decrease)	77.7% (decrease)	1,562% (increase)

ΔP_{pl} = general pressure measurement (pulmonary pressure)

R_L = resistance in cm H20/L/sec

C_{dyn} = dynamic compliance in L/cm H20

** 16 actuations of Metered Dose Inhaler canister @ 200μg pirbuterol/actuation

Visual confirmation that an aerosolized medicament dose actually reached the horse's lung was accomplished through bronchoscopy. A fiberoptic bronchoscope was inserted into the trachea of the horse

with its tip residing just above the carina. The distal end of the medium sized nasal conduit was then placed in the external nostril of the horse and the canister actuated concurrent with the horse's inspiratory effort. The aerosol cloud was clearly seen to enter both the bronchi of the horse lung. This is evidence that the resultant bronchodilation recorded in Table 1 was in fact due to medicament acting directly on the airways.

EXAMPLE 1

To develop a preferred shape of the nasal conduit (e.g. an anatomically correct shape, 100), a cast of the external nostril and a portion of the internal nasal passageway was initially constructed. To construct the cast, a vinyl polysiloxane (Express™ brand dental registration and impression material, No. 7312, generally available from the Minnesota Mining and Manufacturing Company of St. Paul, Minnesota (3M)) was formed into a six (6) to eight (8) inch tube and was then pressed into the left nasal passageway of a live horse. The material was left in place to harden (approximately six minutes) and then it was removed. The space of the nasal diverticulum was manually removed from the hardened material. The resultant, hardened material represented a negative image of the internal equine nostril except for the nasal diverticulum.

The same impression material was also formed into a flat sheet that was placed over the external nare of the horse using only the force required to form the material over the external anatomy of the horse nare. This second, hardened material represented a negative impression of the external anatomy of the horse nare.

The impression of the external nare anatomy (the second hardened material) was then placed on the surface of freshly prepared patching plaster (Bondex),

anatomy side up, and carefully pressed into the plaster. The plaster was allowed to set and was used as a base for forming the cast.

The impression of the internal nare was then glued to the external nare impression. A tube was then placed over both impressions and filled with liquid silastic (generally available from Dow Corning). The silastic was then allowed to cure for several days until hard. The Express™ casts were then removed from the silastic leaving behind a positive image of the equine nostril and external nare.

This cast was then used to generate the solid form of the equine nasal conduit. Again Express™ (No. 7301H) was injected into the nasal cavity of the cast just beyond the juncture to the diverticulum. The injection process continued backwards toward the opening of the nare until it was just even with the fold for the nasal septum. The tip of a rubber laboratory hydrometer bulb similar to the medium sized bulb described in the test results was cut off such that the opening (internal diameter) coincided with the opening to the external nare of the mold. The opposite end of the bulb has a small hole cut into it so that Express™ could be injected via that port. The bulb was carefully placed onto the Express™ previously injected into the mold and then filled with additional Express™. This was allowed to harden. Once set, the bulb was removed and the entire Express™ casting was removed from the positive mold resulting in a solid bulb-like conduit that had a tapered tip shaped to conform to the internal anatomy of the equine nostril and to the nare.

This solid bulb was laser scanned to generate an electronic three dimensional model using a conventional laser scanner. The electronic data was used to create a three dimensional computer model of the conduit using Unigraphics CAD (Computer Assisted Design) software. The CAD file of the computer model was used as the input data source for a Cubital Rapid

Prototyping System (available from Cubital America Inc., of Warren, Michigan) to create a master model. The master model was placed in a frame. The frame was filled with an RTV silicone polymer which was subsequently cured to provide a silicone mold. The silicone mold was injected with a polyurethane polymer (REN-RP6401 polyurethane, generally available from Ceiba-Geigy of East Lansing, Michigan) and then spun along various axes to distribute the urethane over the inner surface of the mold (rotational molding). After the urethane had set, the halves of the mold were separated to provide a hollow cast of the equine nasal conduit 100.

The present invention has now been described with reference to several embodiments thereof. It will be apparent to those skilled in the art that many changes or additions can be made in the embodiments described without departing from the scope of the present invention. For example, a suitable alternative apparatus may comprise a hollow tube 40 with an orifice 42 located generally adjacent the distal end 26 of the conduit 10 in the manner shown in U.S. Patent No. 5,231,983.

WHAT IS CLAIMED IS:

1. Apparatus adapted to be at least partially inserted into a nostril of a large animal such as a horse for administering an aerosol to the large animal, the apparatus being adapted for use with an aerosol generating device, the apparatus comprising:

a conduit having outer surfaces, a proximal end, a distal end having an outlet, and inner surfaces affording passage of an aerosol generated by the aerosol generating device through the conduit,

the inner surfaces defining a lumen extending between the proximal and distal ends and opening to said outer surfaces at said outlet;

the conduit having a length which affords locating the outlet in the nasal passageway of the large animal; and

connecting surfaces for connecting the conduit to the aerosol generating device so that the outlet of the conduit may be placed in fluid communication with the aerosol generating device.

2. In combination, an aerosol generating device for generating a respirable aerosol, and a conduit for administering the respirable aerosol to the large animal, the conduit comprising:

outer and inner surfaces, a proximal end, and a distal end having an outlet,

the inner surfaces defining a lumen extending between the proximal and distal ends and opening to said outer surfaces at said outlet;

the conduit having a length which affords locating the outlet in the nasal passageway of the large animal; and

means for connecting the conduit to the aerosol generating device so that the outlet of the conduit is in fluid communication with the aerosol generating device.

3. An apparatus according to claims 1 or 2 wherein the large animal has a nasal diverticulum, and when the conduit is fully inserted into the nostril of the large animal, the conduit has a sufficient length to avoid situating the outlet such that it opens in a position that allows passage of the aerosol into the nasal diverticulum of the large animal.

4. An apparatus according to claims 1 or 2 wherein the conduit has first and second sections, with the outlet situated in the second section and with the connecting surfaces situated in the first section.

5. An apparatus according to claim 4 wherein the first and second sections of said conduit have cross-sections,

wherein the cross-sectional area of a cross-section in the first section is generally larger than the cross-sectional area of a cross-section in the second section so that inner surfaces of the first section of the conduit form an expansion chamber to afford expansion of the aerosol.

6. An apparatus according to claim 4 wherein the first section is generally bulbous shaped.

7. An apparatus according to claims 1 or 2 wherein said conduit is constructed from a flexible, resilient material adapted to generally conform to the large animal's nasal passageway, and to restrict collapse when a portion of the conduit is placed in the nasal passageway of the large animal so that the outlet remains in fluid communication with the aerosol generating device.

8. An apparatus according to claim 1 wherein the aerosol comprises a respirable aerosol.

9. An apparatus according to claims 1 or 2 wherein said outer surfaces of said conduit comprise:

sealing surfaces adapted to abut the tissue surrounding the nostril of the large animal so that substantially all of the inspiratory airflow through the nostril is directed through the lumen of the conduit.

10. An apparatus according to claim 1 wherein the conduit affords passage of aerosol in generally the same direction as the inspiratory airflow through the nostril.

11. An apparatus according to claims 2 or 10 wherein: when the conduit is fully inserted into the nostril of the large animal, the inspiratory airflow through the nasal passageway at the location of the outlet defines a first direction, and

the conduit affords passage of the aerosol through the outlet in a direction that is generally parallel to the first direction.

12. An apparatus according to claims 1 or 2 wherein the lumen has a central axis extending from the connecting surfaces to the outlet, and the portion of the axis generally adjacent the connecting surfaces is situated at approximately a right angle with respect to the portion of the axis generally adjacent the outlet.

13. An apparatus according to claims 1 or 2 wherein the outer surfaces are irregular shaped to conform to the irregular shaped surfaces of the large animal's nasal passageway.

14. A combination according to claim 2 wherein the first and second sections of said conduit have cross-sections,

wherein the cross-sectional area of a cross-section in the first section is generally larger than the cross-sectional area of a cross-section in the second section so that inner surfaces of the first section of the conduit form an expansion chamber to afford expansion of the respirable aerosol.

15. A combination according to claim 2 wherein the aerosol generating device comprises a canister of the type for dispensing a metered dose of a respirable aerosol medicament through a hollow stem when the stem is actuated, and

the means for connecting the conduit to the aerosol generating device comprises:

a body having an air passageway adapted to be in fluid communication with the lumen of the conduit, and an air opening, the body including:

a stem receptacle generally adjacent the air passageway for receiving the stem of the canister,

means for mounting the canister for movement relative to the stem to actuate the stem; and

a hollow tube communicating with a hollow stem in the stem receptacle, the hollow tube having an outlet opening into the air passageway for delivering a metered aerosol dose to the air passageway for administration through the conduit to the large animal.

16. A combination according to claim 15 wherein the body includes a handle which affords a pistol-like grip, and

a trigger movable between a cocked and fired position.

17. A combination according to claim 16 further including means for moving the canister relative to the stem when the trigger is moved from the cocked toward the fired position so that the trigger may actuate the stem.

18. A combination according to claim 15 wherein the body includes means for detachably attaching the canister to the body.

19. A method of administering a respirable aerosol to a large animal such as a horse comprising the steps of:

(1) providing an aerosol generating device capable of generating a respirable aerosol upon actuation;

(2) providing a conduit comprising:

outer and inner surfaces, a proximal end, and a distal end having an outlet, the inner surfaces defining a lumen extending between the proximal and distal ends and opening to said outer surfaces at said outlet; the conduit having a length which affords locating the outlet in the nasal passageway of the large animal;

(3) connecting the conduit to the aerosol generating device so that the outlet of the conduit is in fluid communication with the aerosol generating device;

(4) inserting the distal end of the conduit into the nostril of the large animal; and

(5) then actuating the aerosol generating device to deliver the respirable aerosol.

20. A method according to claim 19 wherein the large animal has a nasal diverticulum, and

the step of inserting the distal end of the conduit into the nostril comprises the step of:

inserting the conduit sufficiently far into the nasal passageway to avoid situating the outlet such that it opens in a position that allows passage of the aerosol into the nasal diverticulum of the large animal.

21. A method according to claim 19 wherein the step of providing a conduit comprises the step of providing outer surfaces which generally conform to the tissue of the large animal's nasal passageway.

22. A method according to claim 19 wherein the step of inserting the distal end of the conduit into the nostril comprises the step of:

sealing the tissue surrounding the nostril of the large animal with sealing surfaces of the conduit so that substantially all of the inspiratory airflow through the nostril is directed through the lumen of the conduit.

23. A method according to claim 19 wherein the step of actuating the aerosol generating device to deliver the respirable aerosol comprises the steps of:

flowing inspiratory airflow through the nasal passageway at the location of the conduit outlet in a first direction, and

directing passage of the respirable aerosol through the outlet in a direction that is generally parallel to the first direction.

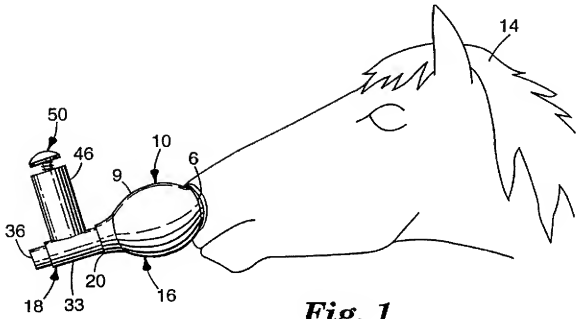


Fig. 1

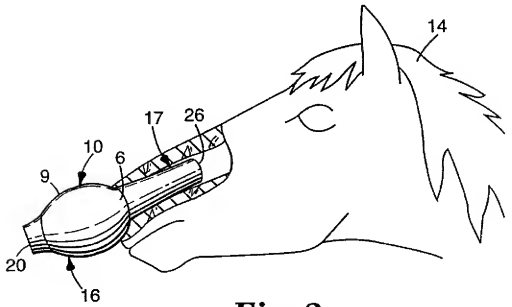


Fig. 2

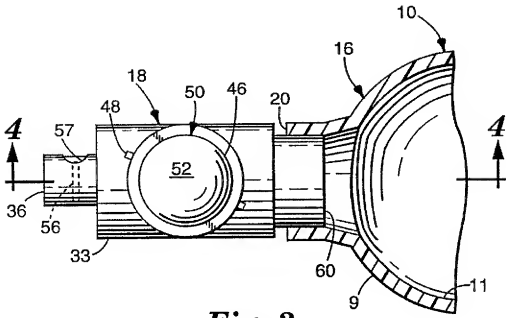

10
16
18
50
46
20
48
4
57
52
4
36
56
33
60
9
11

Fig. 3

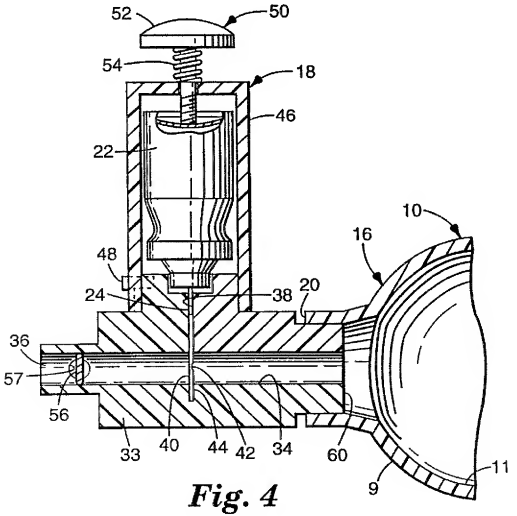

52
50
54
18
46
22
10
16
48
24
38
20
36
57
56
33
40
44
42
34
60
9
11

Fig. 4

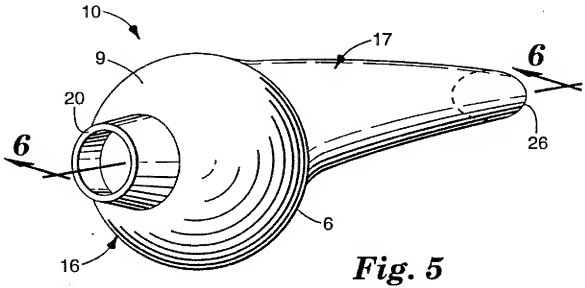


Fig. 5

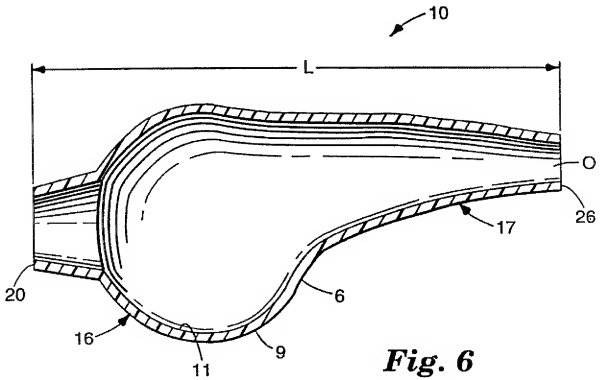


Fig. 6

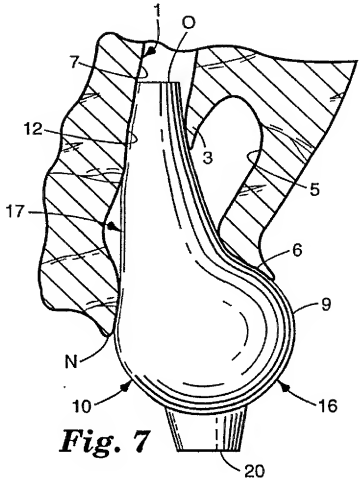

1
O
7
12
3
5
17
6
9
N
10
16
20

Fig. 7

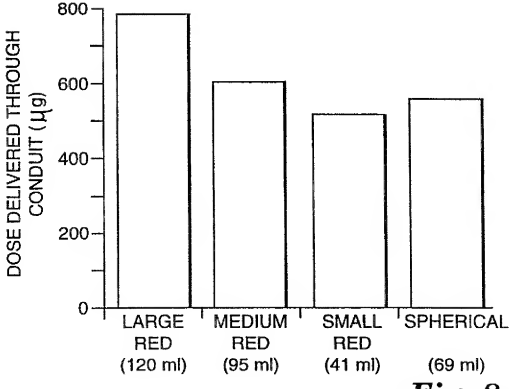

DOSE DELIVERED THROUGH CONDUIT (µg)
800
600
400
200
0
LARGE RED (120 ml)
MEDIUM RED (95 ml)
SMALL RED (41 ml)
SPHERICAL (69 ml)

Fig. 8

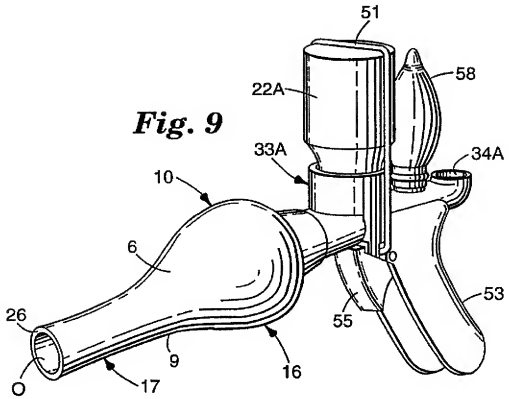

51
58
22A
33A
34A
10
6
53
55
26
9
16
17

Fig. 9

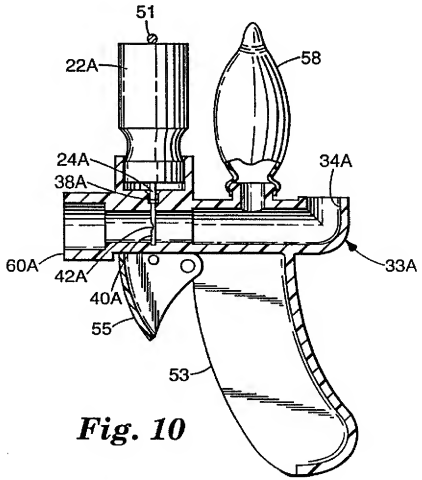

51
22A
58
24A
34A
38A
60A
42A
33A
40A
55
53

Fig. 10

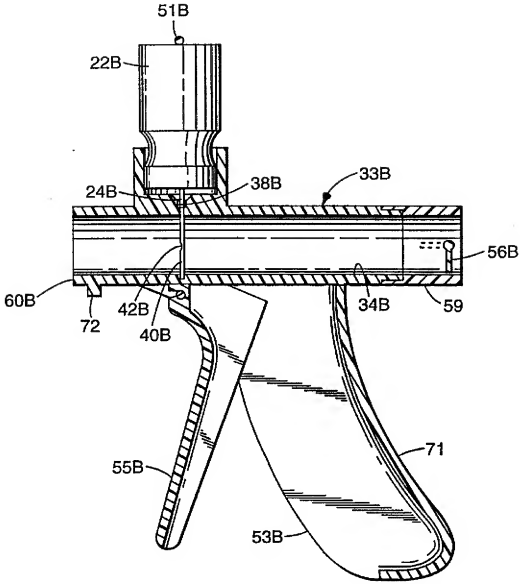


Fig. 11

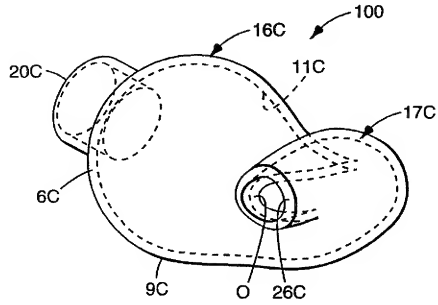

100
16C
20C
11C
17C
6C
9C
O
26C

Fig. 12

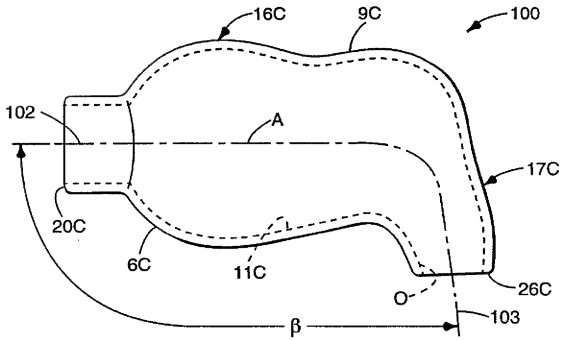

16C
9C
100
102
A
17C
20C
6C
11C
26C
O
103
β

Fig. 13

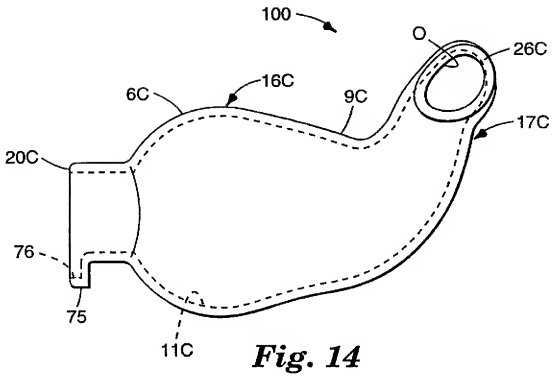


Fig. 14

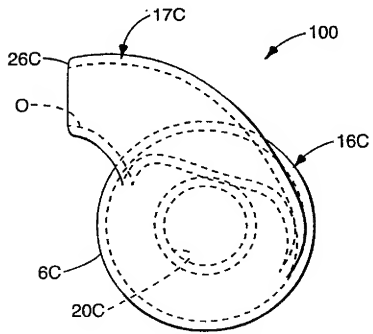


Fig. 15

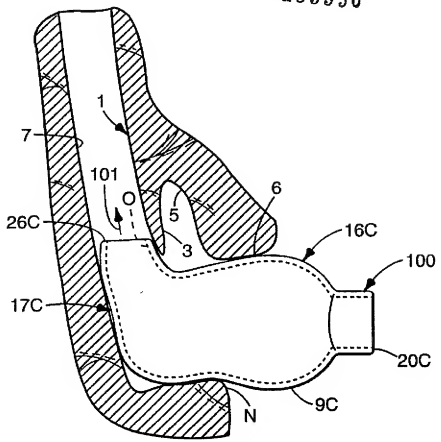


Fig. 16

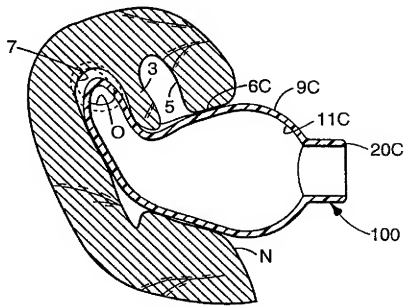


Fig. 17